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Echocardiographic "Smoke" Is Produced by an Interaction of Erythrocytes and Plasma Proteins Modulated by Shear Forces

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Objectives. This study was designed to determine the blood elements responsible for spontaneous echocardiographic contrast.

Background. Spontaneous contrast or "smoke" is an echocardiographic image usually found in low flow conditions. Two blood elements, erythrocytes and platelets, have been related to the generation of smoke.

Methods. The echogenicity of porcine blood products was assessed in static and flow conditions and was graded on a digitized videodensity computer program that assigned a score of 0 for black and 100 for white images. Blood elements were circulated from a small tube (4-mm diameter) into a larger cylindric chamber (30-mm diameter) under controlled flow rate conditions. The following blood products were studied: whole blood, platelet-depleted blood, platelet-rich plasma, platelet-poor plasma, erythrocytes suspended in saline solution, adenosine diphosphate (ADP) added to platelet-rich plasma, and saline solution as a control medium.

Results. As blood flow was increased in 30 ml/min increments from 0 to 180 ml/min, whole blood echo videodensity (scale 0 to 100) progressively decreased in the larger tube from 38 and 42 to 20, 12, 14, 16 and 14, respectively. When flow increased from 0 to 30 ml/min in the smaller tube, corresponding to a wall shear rate of 0 to 80 s^{-1}, the blood entering the chamber was completely echolucent. The echogenicity of blood products in the larger tube was for static flow (0 ml/min) and high flow (180 ml/min), respectively: platelet-depleted blood = 36 and 14; platelet-rich plasma = 2 and 2; platelet-poor plasma = 0 and 0; erythrocytes in saline solution = 8 and 12; ADP added to platelet-rich plasma = 0 and 15; saline solution = 0 and 0. Because platelets alone were nonechogenic but platelet-depleted blood produced a flow-dependent echogenicity similar to that produced by whole blood, platelets may not be involved in the production of smoke. However, when platelets were aggregated by ADP, they were echogenic but in dense clumps and in a flow-independent pattern not typical of the smokelike images. Erythrocytes suspended in saline solution had an intermediate density image.

Conclusions. Echogenic smoke appears to be due primarily to the interaction of red blood cells and plasma proteins at low flow and low shear rate conditions.

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Spontaneous contrast or "smoke" is an echocardiographic finding defined as an amorphous, swirling, light gray haze inside the left and right heart chambers, great vessels and veins, attributed to conditions of blood stasis (1–5). Blood stasis and the presence of smoke in the left ventricle or left atrium have been associated with thrombus formation and systemic embolism in clinical studies (1,2,4–6).

Though two blood components, red blood cells and platelets, have been implicated in the pathogenesis of spontaneous contrast (7–13), there are no definitive studies simulating clinical conditions. Therefore, we sought to generate spontaneous contrast in an in vitro model and to compare the ability of blood elements, alone and in combination, to generate smoke in static and flow conditions.

Methods

In Vitro Model for the Reproduction of Spontaneous Contrast

Procedure. Blood freshly drawn from 3-month old Yorkshire albino pigs (24 to 32 kg), anticoagulated with 1:10 90-m*M* sodium citrate, was circulated by a peristaltic pump through a narrow (4-mm diameter) plastic tube into a cylindric expansion chamber (30-mm diameter) (Fig. 1). A 7.5-MHz linear transducer (Acuson) was applied longitudinally to the chamber and fixed in position. The video images were recorded on a high resolution VHS recorder. Swine blood was selected for these experiments because of the

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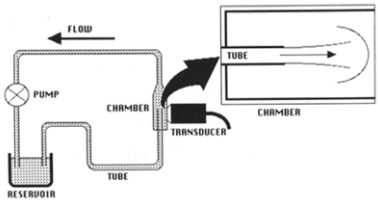


Figure 1. Diagram of the in vitro circulation system. Top right, Longitudinal section of the chamber and the tube at the inflow port, as seen in the echographic images.

similarity of the human and porcine coagulation systems and the comparable red cell aggregation, as opposed to that of other animal species (14,15). The management of experimental animals conformed to the "Position of the American Heart Association on Research Animal Use."

Definition of spontaneous contrast. Echogenic smoke was defined according to the previously reported clinical description (2,7), which requires 1) low amplitude echogenic haze; 2) slow, repetitive movement in the cavity; and 3) dissipation and disappearance of the image when blood flow increases and reappearance as flow decreases.

Flow and shear rate conditions. Echocardiographic images were obtained first in static conditions (0 ml/min flow rate) and then consecutively at flow rates of 30, 60, 90, 120, 150 and 180 ml/min. Shear rate was calculated by assuming laminar Newtonian flow conditions in the small tubular chamber. At physiologic shear rates >100 s^{-1}, blood can be considered a Newtonian fluid with constant viscosity (16,17). However, even at shear rates of 50 to 100 s^{-1}, the deviation of viscosity from the Newtonian values is small (16). The wall shear rates were calculated from the expression for shear rate given for a Newtonian fluid in tubular flow (18). In all experiments, the echodensity of the chamber was calculated at every flow and shear condition.

In the expansion chamber, the local shear conditions are complex and could not be easily determined because flow streamlines are not parallel. However, to estimate the magnitude of the shear conditions, we calculated the wall shear rate in a tube of equivalent dimensions (30-mm diameter) at maximal diameter of the central jet (10 mm) and with assumption of steady laminar flow. As shown in Table 2, the shear conditions ranged from double digits to less than that observed in the small tubular chamber. Such conditions are intended to represent grossly the mixed flow encountered in cardiac chambers, although obviously no attempt was made to precisely simulate these conditions in the present study.

Echographic analysis. Gain and depth before and after processing and log compression were maintained constant throughout all experiments. The images were recorded on 0.5-in. (1.27 cm) videotape for subsequent analysis by two independent observers on a digitizing echoanalyzer (Nova-Microsonics) that graded gray scale videodensity as 0 for a black image or absence of echoes and 100 for maximal echodensity or white image. Then, a 2-cm perpendicular line was positioned 1 cm from the blood flow inlet for all measurements (Fig. 1). The gray scale videodensity along the entire digitized line was averaged, producing a single number.

Table 1. Blood Composition and Echodensity of the Different Experiments

Experiment	RBC (× 10^6/mm^3)	Hct (%)	Platelets (/mm^3)	Echodensity (ml/min) 0	180
Whole blood					
A1	4.87	21	362,000	35	14
Erythrocytes in plasma					
B1	3.01	16	14,000	39	12
B2*	4.53	20	21,000	36	14
B3	8.73	37	34,000	10	8
B4	13.2	50	56,000	8	6
Platelets in plasma					
C1	0	0	13,000	0	0
C2	0.32	0	120,000	0	0
C3	0.1	0	497,000	0	0
C4†	0.25	0	1,170,000	2	2
Erythrocytes in saline solution					
D1	2.37	10	4,000	12	13
D2‡	4.16	18	4,000	8	12
Saline solution					
E	saline	—	—	0	0
Whole blood + ADP					
F	4.87	21	362,000	35	14
Platelet-rich plasma + ADP					
G	0.25	0	1,170,000	0	15

*Platelet-depleted blood. †Platelet-rich plasma. ‡Washed red blood cells. ADP = adenosine diphosphate; Hct = hematocrit; RBC = red blood cells.

Study of Blood Components

To determine which components of blood contribute to the generation of spontaneous contrast, we studied the main components of blood: red cells, platelets and plasma, individually and in different combinations. Leukocytes were excluded because they account for <1% of blood. The characteristics of each experiment are detailed in Table 1.

Whole blood. Whole pig blood with a physiologic combination of red cells, platelets and plasma (hematocrit = 21%; platelets = 362 × 10^3/mm^3; red blood cells = 4.87 × 10^6/mm^3) was studied intact without alteration except for the use of anticoagulants.

Red blood cells + plasma. Whole blood was centrifuged at 800 rpm for 10 min at room temperature. The platelet-rich supernatant was discarded. The erythrocyte pellet and platelet-poor plasma were centrifuged again to eliminate the remaining platelets from the red cell supernatant and platelet-poor plasma pellet. Red cells were resuspended in

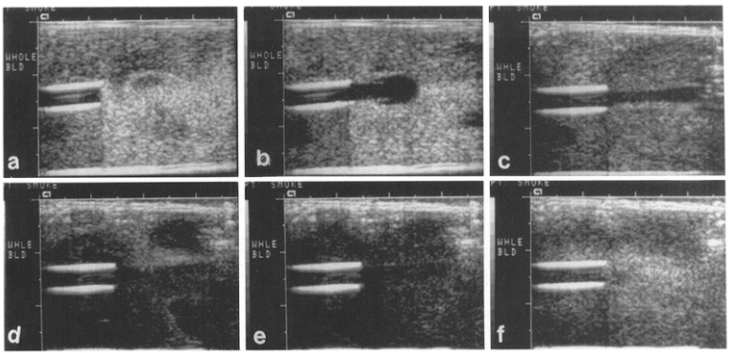


Figure 2. Whole blood (red blood cells = 4.87 × 10^6; hematocrit = 21%; platelets = 362,000/mm^3) sequence from static to flow conditions: **a**, At a flow rate of 0, blood is highly echogenic. **b**, At a rate of 30 ml/min, blood entering the chamber is completely echolucent. **c**, At 60 ml/min, the blood density in the chamber begins to decrease. **d**, At 90 ml/min, static blood in the chamber periphery produces typical smokelike flow lines. **e**, At 180 ml/min, the chamber is almost echolucent. **f**, At 30 s after flow interruption, the blood slowly regains the initial density. There is an attenuation of the ultrasound beam under the small caliber tube, which should not be confused with a low density area. WHLE BLD = whole blood.

the platelet-poor plasma and were studied at four hematocrit levels ranging from 16% to 50% (Table 1).

Platelets + plasma. Whole blood was centrifuged at 800 rpm for 10 min at room temperature. The platelet-rich supernatant was extracted and mixed with platelet-poor plasma to obtain four levels of platelet concentration ranging from 13 × 10^3/mm^3 to 1.17 × 10^6/mm^3 (Table 1).

Red blood cells (washed erythrocytes in saline solution). Whole blood was centrifuged at 2,500 rpm at room temperature for 15 min. Platelets and plasma were discarded and the erythrocytes were resuspended in saline solution at two concentrations (2.37 10^6/mm^3 and 4.16 × 10^6/mm^3).

Control. Saline solution (0.9% sodium chloride) was used as a control.

Interventions on Blood Elements

Adenosine diphosphate (ADP) was added to the reservoir (Fig. 1) in the following experiments: 1) whole blood + ADP (ADP [20 μg/ml of blood] was added to whole blood); 2) platelet-rich plasma + ADP (ADP [20 μg/ml]) was added to platelet-rich plasma ([platelets = 1.17 × 10^6/mm^3; red blood cells = 0.25 × 10^6/mm^3]).

Results

Whole blood (experiment A1, Table 1, Fig. 2 and Fig. 6). Whole blood imaged under static conditions (0 ml/min flow rate) produced a homogeneous echogenic, grainy haze throughout the cylindrical chamber, which had a high video-density (38 of a maximal score of 100) (Fig. 2a). At flow rates >30 ml/min (corresponding to a wall shear rate >80 s^{-1} in the tube, Table 2), the blood entering the chamber was completely echolucent, creating a clear demarcation between the inflowing blood and the static blood (Fig. 2b). At a flow rate of 30 ml/min (estimated average shear rate = 5 s^{-1} in the chamber), the incoming blood lost its lucency, slowly regaining echodensity. As flow rate was increased (to 60 to 90 ml/min), the typical swirling repetitive images of flow lines were visualized inside the chamber with a corresponding decrease in average density from 42 to 14 (Fig. 2, c and d). At flow rates >180 ml/min (shear rate in the tube = 478 s^{-1}), the region of the chamber distal to the inflow jet became almost echolucent and a central area completely free of smoke, presumably due to the jetting action of the

Table 2. Shear Rate in the Tube and Chamber at Different Flow Rates

Flow (ml/min)	Shear Rate (s^{-1})		
		Chamber	
	Tube	Jet	Periphery
30	80	5	0.19
60	160	10	0.38
90	234	15	0.57
120	318	20	0.75
150	398	25	0.94
180	478	31	1.13

incoming fluid (Fig. 2e), was observed. Blood in the expansion tube chamber was drawn into the streamlines of the laminar flow jet, gradually accelerated and dissolved into the jet stream (Fig. 2, d and e). When the flow was abruptly terminated, the echogenic grainy haze reappeared throughout the chamber within 30 s, slowly regaining the initial high echogenicity score (Fig. 2f).

Erythrocytes and plasma (experiments B1 to B4, Table 1). The four concentrations of red blood cells in plasma generated varied videodensities in static conditions. Red cell concentrations (3.01 and 4.53 × 10^6/mm^3) corresponding to that typically encountered in the experimental animal produced almost identical videodensities to those of whole blood (39 and 36, respectively). However, as red cell concentration increased above these values, there was a dramatic decrease in echodensity (experiments B3 and B4). As for whole blood, with increasing flow rates, there was a corresponding decrease in the echogenicity of the two physiologic red cell concentrations (experiments B1 and B2, Table 1; platelet-depleted blood, Fig. 6).

Platelets and plasma (experiments C1 to C4, Table 1). Platelets suspended in plasma were studied at four concentrations ranging from 5% to 400% of the physiologic level. At 0 flow, all platelet concentrations were echolucent. Only the highest platelet concentration (C4) produced a minimal echo level (2 of a maximum of 100) on the videodensity scoring system. Under flow conditions, the platelet preparations remained entirely echolucent (Table 1; Fig. 3, platelet-rich plasma in Fig. 6).

Erythrocytes (experiments D1 and D2, Table 1). Isolated, washed red blood cells resuspended in saline solution at low and physiologic concentration produced an intermediate echodensity, approximately one third that of static whole blood. There was no alteration in echodensity at high flow rates (Fig. 4, washed red blood cells in Fig. 6).

Control. (experiment E, Table 1). Saline solution (control) studied at static and high flow rates was entirely echolucent in the expansion chamber.

Whole blood + ADP (experiment F, Table 1). When ADP was added to whole blood, small isolated aggregates were imaged, which did not alter the mean videodensity of the blood with respect to experiment A. On the contrary, the decrease in videodensity with an increase in flow rates was identical to the pattern of whole blood in experiment A.

Platelet-rich plasma + ADP (experiment G, Table 1). Because platelets have previously been hypothesized to cause smoke, we initially evaluated platelets in the absence of red blood cells at physiologic concentration and in platelet-rich plasma, but neither solution was echogenic. Even when ADP was added to the reservoir, smoke was not generated (Fig. 5) at the highest concentration of platelets studied (C4). Instead, large irregularly shaped masses (macroaggregates of platelets) entered the chamber through the inflow tube and did not break up even at the highest flow rates. Therefore, the average videodensity of platelet-rich plasma and ADP did not decrease at high flow rates (average echodensity = 15) (platelet-rich plasma + ADP, Fig. 6).

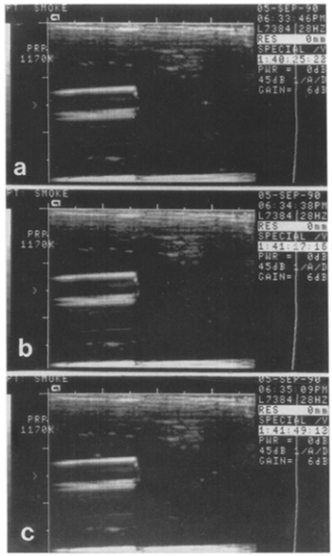


Figure 3. Platelet-rich plasma (PRP) (red blood cells = 0.25 × 10^6; hematocrit = 0%; platelets = 1.17 million/mm^3) sequence from static to flow conditions. **a**, Flow = 0 ml/min. **b**, Flow = 60 ml/min. **c**, Flow = 180 ml/min. Nonphysiologically high concentrations of platelets did not produce echogenicity.

Discussion

Cardiac chambers and blood vessels are usually echolucent. However, the terms "dynamic intracavitary echoes," "smoke" and "spontaneous echocardiographic contrast" describe a wafting swirling haze that is occasionally seen in great vessels and dilated cardiac chambers under conditions of blood stasis (1–5). Spontaneous contrast can be seen in the left atrium of patients with significant mitral stenosis (particularly those with a dilated left atrium and atrial fibrillation) and in the left ventricle and aorta during conditions of low cardiac output (1–5). The features that define smoke are 1) multiple instances of low amplitude echogenic swirling haze; 2) slow, repetitive movement in the cavity; and 3) disappearance when blood flow increases, as when

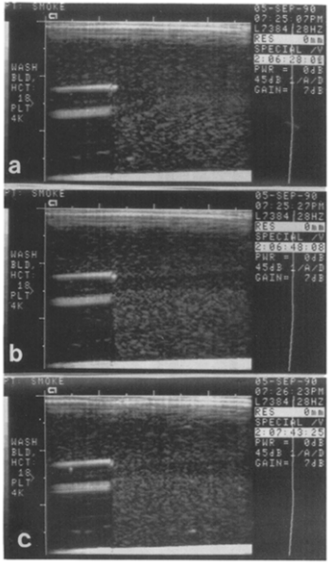


Figure 4. Washed red blood cells (WASH BLD) resuspended in saline solution (washed red blood cells = 4.16×10^6; hematocrit [HCT] = 18%; platelets [PLT] = 4,000/mm^3) sequence from static to flow conditions. a, Flow = 0 ml/min. b, Flow = 30 ml/min. c, Flow = 180 ml/min. Washed red cells had an intermediate videodensity in static conditions. At high flow rates (b and c), there is no decrease in the initial density.

blood enters another cavity (left ventricle, in mitral stenosis) or when conditions of blood stasis are resolved (after surgery for mitral stenosis or dopamine administration to improve contractility in a dysfunctional left ventricle [2,3,7]). Clinically, the presence of spontaneous contrast has been proposed as a potential marker and possible precursor of thrombus formation. Although previous studies (7–13) have described the prevalence and potential clinical significance of spontaneous contrast, speculation continues on the potential role of red blood cells, platelets and plasma components and the mechanisms responsible for echogenic smoke (7–13). We attempted to address this issue by simulating clinical conditions with use of an in vitro flow model emulating pulmonary vein flow into the left atrium or mitral flow into the left ventricle. We also evaluated the potential of various blood components to produce spontaneous contrast.

We found that spontaneous contrast was the result of a flow-related interaction between red blood cells and plasma proteins, independent of platelets.

In vitro model for the reproduction of spontaneous contrast. The distinctive aspect of smoke is the flow lines observed in cardiac chambers. Our in vitro model for smoke production sought to re-create an inflow chamber similar to that of the pulmonary vein into the left atrium. Therefore, we used a small caliber tube emptying into a larger Lucite chamber with a distal outlet (Fig. 1). The peristaltic pump rate could be varied to gradually increase or decrease flow velocity. At low flow rates, blood entering the chamber was echolucent, thus creating a smoke effect similar to that seen in the left atrium by the pulmonary vein flow.

In contrast to other investigators (19,20), we found an initial increase in average echodensity that could be due to the compression of the static blood in the chamber by the incoming jet (Fig. 2b and 6). This difference is probably an effect of the shape of the chamber used. Ours had a small outflow port, which precluded rapid displacement of the blood.

As flow rate increased, the density of whole blood began to dissipate and the inflow jet flow lines generated swirling in the lateral aspects of the jet (Fig. 2). The most dramatic decrease in videodensity occurred when shear rate increased from 10 to 15 s^{-1}. With increasing inflow velocity, the static echogenic smoke was drawn into the main jet stream, thereby decreasing its echogenicity. Similarly, smoke in the left atrium is initially distinct when entering into the left ventricle but dissipates quickly with each systolic contraction. Additionally, left atrial smoke frequently disappears when flow increases after mitral valve replacement or after repair for mitral stenosis, an observation consistent with the importance of low flow in the generation of smoke.

Because blood flow was laminar in the tubing of the system it was possible to make accurate shear rate calculations. Flow was laminar in the central part of the chamber; however, vortexes and recirculation zones were present in the periphery. The shear rate in the chamber was estimated for this central zone and the periphery (Table 2). It is important to emphasize that shear rate, not flow, was the factor related to smoke production, as the flow was identical for both the tubing and the chamber; however, smoke was seen only in the chamber, where shear conditions were several orders of magnitude lower (Fig. 2, b and c).

Mechanism of spontaneous contrast formation. We also sought to isolate the specific flow conditions and the specific blood components involved in smoke formation. We were able to echocardiographically produce smoke that was identical to the pattern seen clinically by transesophageal echocardiography in the left atrium or other cardiac chambers. Thus, we were confident that our model was adequate to test the conditions for the formation of the spontaneous contrast.

Spontaneous contrast was visualized only in whole blood and in physiologic concentrations of red blood cells in plasma. Platelets alone, plasma alone, platelets and plasma,

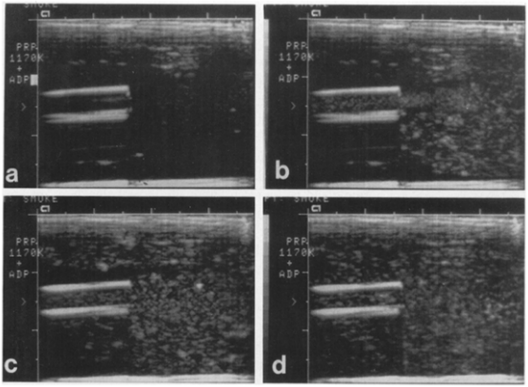
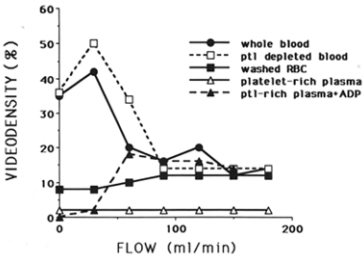


Figure 5. Platelet-rich plasma (PRP) + adenosine diphosphate (ADP) (red blood cells = 0.25×10^6; hematocrit = 0%; platelets = 1.17 million/mm^3) sequence from static to flow conditions. a, Flow = 0. b, Flow = 30 ml/min. c, Flow = 180 ml/min. d, 30 s after flow interruption. At 0 flow, the tube and the chamber are echolucent because ADP was added to the reservoir and not to the chamber. At 30 ml/min, highly echogenic masses are entering the chamber, which is not yet occupied by them. At the highest flow rate (180 ml/min), the masses do not dissolve and occupy the whole chamber.

or very high red blood cell concentrations did not produce spontaneous contrast (Table 1, Fig. 6). Therefore, we conclude that at physiologic concentrations, a red blood cell and plasma protein interaction was responsible for the production of spontaneous contrast.

Figure 6. Average videodensity in the chamber in relation to flow rate of the most significant blood products studied. Standard error of the mean is not expressed in the graph because it was $<\pm 2$ videodensity points in all points. Only platelet-depleted blood had the same density-decrease pattern as that of whole blood. Resuspended red blood cells in saline solution had an intermediate density that was not affected by flow increases. High platelet concentration in plasma did not produce echogenicity. Only when adenosine diphosphate (ADP) was added to the reservoir did the average chamber density increase, producing a paradoxic effect on the characteristic flow-related decrease in density observed in spontaneous contrast. These findings suggest that blood echodensity is due to an interaction of red blood cells and plasma that is platelet independent. Whole blood corresponds to experiment A1 in Table 1. Platelet-depleted blood corresponds to E2, washed red blood cells (RBC) to D2, platelet-rich plasma to C4 and platelet (ptl)-rich-plasma + ADP to G.



The importance of red blood cells in generation of smoke is consistent with previous studies (21,22) on blood rheology showing that these cells form small aggregates in low shear conditions (<10 s^{-1}) that are easily dispersed when shear rate increases. In static conditions, erythrocytes form "rouleaux" (parallel alignment of cells) and then, these rouleaux rearrange to form spheric aggregates (22). The mechanism of red cell aggregation is very complex because of the characteristic shape of the membrane and the complex electrical charge structure. Erythrocytes repel each other by negative surface electrostatic forces but are also attracted to each other by electrodynamic phenomena or the van der Waals forces. The latter forces are weak attracting forces between the electric dipole moments of atoms or molecules that in turn can induce dipole moments in neighboring molecules. However, the magnitude of these forces is small in relation to the energy of the Brownian motion that precludes the formation of stable structures or aggregates. The formation of erythrocyte aggregates or "rouleaux" requires the presence of macromolecules in the medium such as plasma alpha- and beta-globulins and fibrinogen; these proteins establish reversible bridges among red blood cells. We found a progressively decreasing videodensity at hematocrit levels >40%. Interestingly, the "rouleaux" phenomenon is less important at high hematocrit levels and does not take place when hematocrit is >70%. The weak nature of this protein binding explains the reversibility of the aggregates and may account for the transient nature of spontaneous contrast. Shear stress, which is the product of the velocity gradients between parallel flow lines located in the

center and the periphery of blood vessels times the blood viscosity, exerts a mechanical force on red cell aggregates that overcomes the weak attracting forces, thus maintaining the erythrocyte separation in flowing conditions.

Shear rate has been grossly estimated to be as low as 2 to 9 s^{-1} in the left atrium in severe mitral stenosis and in the dilated aneurysmal left ventricle (2). These extremely low shear conditions (<2 s^{-1} in our experiments) may permit red cell aggregation and thus the visualization of blood flow lines known as smoke. In an elegant experiment, Mikell et al. (7) produced spontaneous contrast in the left ventricle of a dog by ligating the anterior descending artery and producing an aneurysm. In this same experiment, smoke disappeared when left ventricular contractility was increased with the infusion of dopamine. In addition, when asystole was produced by intravenous administration of potassium chloride, the whole left ventricle was filled with an echogenic image that showed a sludgelike movement image by external compression of the heart.

Using real time imaging, Sigel et al. (9,19) also found that red cells in plasma were echogenic as opposed to washed red cells resuspended in saline solution. The same investigators reported that blood echogenicity was related to the shear rate and the frequency of the transducer used. In an experimental setting similar to ours, Yuan and Shung (20,23) demonstrated that the ultrasound backscatter from flowing blood was affected by shear rate. However, they did not study blood components separately in a control model. We demonstrated that platelet-depleted blood and whole blood had the same shear-related echogenicity, whereas neither red cells in saline solution nor extremely high concentrations of platelets in plasma were able to do so. Therefore, red cell aggregation is probably responsible for smoke production.

Platelet aggregates. Because of the potential relation between thrombus formation and smoke, some studies hypothesized that platelet microaggregates cause spontaneous contrast (10,11). In our experiment, platelets in plasma without red blood cells produced an echo-free image. Regardless of the platelet count (from 13,000 to 1.17 million platelets/mm^3) the videodensity of the image was identical to that of plasma alone or that of saline solution (Fig. 3 and 6). Therefore, platelets do not contribute to the echogenicity of blood in static conditions even at nonphysiologic concentrations. Platelet aggregates induced by ADP produced an echogenic image in static conditions. However, these echoes correspond to irreversible platelet clumps and not to the characteristic reversible smoke image. Mahony et al. (11) reported that spontaneous contrast was induced in the canine right ventricle by the administration of ADP, thus suggesting that smoke is due to platelet microaggregates. They reported that spontaneous contrast was seen as a cloud of echoes passing through the right chambers of the canine heart, and immediately after, the dog had dyspnea and oxygen desaturation, suggesting lung embolization. These echoes probably correspond to platelet clumps induced by ADP and do not conform to the characteristics of reversible spontaneous contrast.

Conclusions. Spontaneous contrast is an echocardiographic image seen in low flow states that has been associated with thrombus formation. In a flow model simulating clinical conditions, we determined smoke to be a red blood cell-plasma protein interaction that is platelet independent and shear dependent, probably because of red cell aggregation. Both intracavitary thrombosis and smoke are found in low output states. Although anticoagulation can prevent thrombosis, it does not affect smoke formation. Because of the clinical relevance of intracavitary thrombosis, the interrelation between these two processes needs to be clarified.

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